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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/765,466 | 01/26/2004 | Sachiko Machida | 690115.401C1 | 8356 |

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| EXAMINER |
|---|
| YU, MELANIE J |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/765,466 | MACHIDA ET AL. | |
| | Examiner | Art Unit | |
| | Melanie Yu | 1641 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *07 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,15-17,44 and 45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,15-17,44 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. Applicant's amendment filed 7 June 2007 has been entered.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham **v.** John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

2. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Holtzman (US 5,969,123) in view of Schatz (US 5,932,433).

Holtzman teaches a biochip for a screening assay (col. 12, lines 7-8) comprising a biotinylated receptor protein immobilized via a factor capable of specifically binding to biotin (streptavidin specifically binds to biotin and the biotinylated proteins is immobilized to the streptavidin, col. 12, lines 8-16), wherein the receptor protein comprises a biotinylation sequence motif (biotinylated protein comprises biotinylation sequence motif, col. 12, lines 11-16), and wherein the receptor protein has the ability of being specifically bound by a ligand of the receptor protein (col. 8, line 65-col. 9, line 6). Holtzman fails to teach the biotinylation of the receptor protein carried out within a bacterial host.

Schatz teaches a recombinantly expressed biotinylated receptor protein immobilized via a factor capable of specifically binding to biotin (peptides are biotinylated and bound to streptavidin which specifically binds to biotin, col. 8, lines 10-27, biotinylated peptide may be a protein, col. 6, lines 13-19), wherein the receptor protein comprises a biotinylation sequence motif (when peptides are biotinylated, they gain a biotinylation sequence motif, col. 8, lines 10-27; col. 4, lines 57-60), wherein the biotinylation of the receptor protein has been carried out within a bacterial host instead of in vitro (carried out in *E. coli* host cells, col. 3, lines 47-50; col. 8, lines 10-14), in order to provide a protein that has been biotinylated.

Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include in the biotinylation of the receptor protein of Holtzman, biotinylation in vivo instead of in vitro as taught by Schatz, in order to provide a simplified biotinylation process (Schatz, col. 2, lines 59-63).

3. Claims 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holtzman (US 5,969,123) in view of Schatz (US 5,932,433) further in view of Tall et al. (US 6,756,228).

Holtzman in view of Schatz teach a biotinylated receptor protein that is immobilized to a substrate via a factor capable of specifically binding to biotin, but fail to teach the receptor specifically being LOX-1.

Tall et al. teach a LOX-1 receptor immobilized to a substrate (col. 12, lines 29-38; col. 11, line 52-col. 12, line 57), in order to detect the presence of LOX-1 activity.

Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include as the receptor protein of Holtzman in view of Schatz, a receptor protein of LOX-1 as taught by Tall et al., in order to provide a substrate that indicates a decreased or increased susceptibility to atherosclerosis.

4. Claims 17 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brigham-Burke et al. (US 5,395,587) in view of Holtzman (US 5,969,123) further in view of Schatz (US 5,932,433).

Brigham-Burke et al. teach a protein immobilized on a SPR substrate (sensor chip, col. 5, lines 29-35; col. 5, lines 10-23) that conforms to a shape of an insertion site of a surface plasmon resonance device (sensor chip fits through a slot in the housing for SPR detection, 14, Fig. 1; col. 5, lines 30-35), but fail to teach the protein being biotinylated and immobilized via a factor capable of binding specifically to biotin.

Holtzman in view of Schatz, as applied to claim 1, teach a biotinylated receptor protein immobilized on a substrate via a factor capable of specifically binding to biotin, in order to provide immobilization of receptor proteins on a substrate.

Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include on the substrate of Brigham-Burke et al., an immobilization technique of a biotinylated receptor protein as taught by Holtzman in view of Schatz, in order to simple and efficient immobilization of proteins on a substrate.

5. Claims 17 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muramatsu (Piezoelectric Crystal Biosensor Modified with Protein A for Determination of Immunoglobulins, 1987, Analytical Chemistry, vol. 59, pages 2760-2763) in view of Holtzman (US 5,969,123) further in view of Schatz (US 5,932,433).

Muramatsu teaches a protein immobilized on a crystal oscillator (pg. 2760, right column, last paragraph), but fail to teach the protein being biotinylated and immobilized via a factor capable of binding specifically to biotin.

Holtzman in view of Schatz, as applied to claim 1, teach a biotinylated receptor protein immobilized on a substrate via a factor capable of specifically binding to biotin, in order to provide immobilization of receptor proteins on a substrate.

Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include on the substrate of Muramatsu, biotinylation of a protein receptor and immobilization via a factor capable of binding specifically to biotin as taught by Holtzman in view of Schatz, in order to simple and efficient immobilization of proteins on a substrate.

***Response to Arguments***

1. Applicant's arguments filed 7 June 2007 have been fully considered but they are not persuasive. Regarding the rejection of the claims under 35 USC 103a, applicant argues that there is no motivation with reasonable expectation of success to combine the references of Holtzman in view of Schatz. Applicant argues that the prior art fails to teach producing functional, refolded proteins that can be oriented identically due to in vitro biotinylation in an amount sufficient to produce receptor chips. Applicant's argument is not persuasive because such limitations are drawn to methods of making the protein and are not required by the claims.

2. Applicant also argues that Schatz does not teach that a protein has been biotinylated in vivo and can maintain its natural activity because the proteins of Schatz are intended to be used only with respect to the biotinylation motif of the protein and not the remaining protein. However, in response to applicant's argument, it is noted that although the biotinylated proteins of Schatz are used to screen for biotinylation enzymes, Holtzman teaches that a protein may be biotinylated in vitro and the functional end of the protein is used to screen for binding proteins and maintains its original function. The difference between the protein of Holtzman and Schatz is that the protein of Holtzman is biotinylated in vitro while the protein of Schatz is biotinylated in vitro or in vivo. The resulting protein of Holtzman retains its original binding functionality for use in screening assays. Therefore the protein of Schatz must be biotinylated in vivo and be used in a screening assay to provide

reasonable expectation of success in a combination with Holtzman. Since the biotinylated protein of Schatz is biotinylated either in vitro or in vivo and is used in screening assays, one having ordinary skill would expect a reasonable expectation of success of biotinylating the proteins of Holtzman in vivo instead of in vitro. Furthermore, at column 12, lines 34-62, Schatz teaches that proteins may be biotinylated so the proteins can bind to receptors and be immobilized to streptavidin coated beads or wells. Therefore, the biotinylated protein of Schatz retains functionality for binding to receptors after biotinylation and it would have been obvious to biotinylate the protein of Holtzman in vivo.

3. Applicant further argues that Schatz does not teach that proteins that are traditionally difficult to express in high amounts can be successfully adapted to an in vitro biotinylation and expression protocol and purified receptor proteins are known to be difficult to produce using in vivo expression techniques. In response to applicant's argument, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

4. Applicant also argues that the presently claimed receptor chip offers surprising advantages over the prior art and Schatz does not teach any advantages associated with in vivo biotinylation in contrast to in vitro biotinylation and suggests that these are simply alternatives. However, applicant's arguments are not persuasive for two reasons. Firstly, Schatz teaches an advantage of in vivo biotinylation instead of in vitro as discussed in the rejection above. Secondly, Schatz teaches that in vivo and in vitro biotinylation are recognized by the prior art as alternative means of biotinylation of a protein and therefore provides further evidence that one having ordinary skill in the art would have had a reasonable expectation of success to biotinylate the proteins of Holtzman in vivo.

5. Applicant argues that Schatz only describes in vivo biontinylation of MBP and never examines whether the MBP can still bind to maltose. Applicant's argument is not persuasive because Holtzman teaches that a biotinylated protein retains its functionality and binds to the target analyte before and after biotinylation. Therefore, the biotinylated protein of Schatz is capable of binding to its target analyte before and after biotinylation.

***Conclusion***

No claims are allowed.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Melanie Yu whose telephone number is (571) 272-2933. The examiner can normally be reached on M-F 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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